## Systemic lupus erythematosus in the elderly finally diagnosed as VEXAS syndrome

Sirs,

The recently described VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is due to an acquired inactivating mutation of the X-linked UBA1 gene (1). Clinically, it is characterised by a combination of inflammatory and haematological manifestations presenting in male patients from the age of fifty years old, typically with a treatment-refractory course and high mortality rates (2, 3). Fever, skin lesions, weight loss, lung involvement, arthralgia/arthritis, relapsing polychondritis, ocular symptoms, venous thrombosis and lymphadenopathy have been commonly described. VEXAS syndrome mimics inflammatory phenotypes such as relapsing polychondritis, Sweet's syndrome, polyarteritis nodosa or giant cell arteritis (1). Herein, we report a case of VEXAS syndrome mimicking systemic lupus erythematosus (SLE).

A 78-year-old man with a long-standing history of persistent thrombocytopenia and leukopenia presented with pruritic erythematous plaques on the face, upper trunk and upper extremities, clinically and histopathologically suggestive of lupus tumidus (Fig. 1A). Treatment with hydroxychloroquine 200 mg/day and topical clobetasol propionate 0.05% ointment was initiated, with little improvement. One year later, the patient presented with bilateral and symmetrical polyarthritis of the hands, feet, elbows and knees. He denied febrile episodes, photosensitivity, oral thrush, Raynaud's phenomenon, dry syndrome or oedemas. Laboratory workup showed leukopenia (3,600/µl), lymphopenia (600/µl), thrombocytopenia (86,000/µl), macrocytic anaemia (haemoglobin 10 g/dL; MCV 100.4 fL) and an elevated erythrocyte sedimentation rate (ESR) (80 mm/hr). Antinuclear antibodies (ANA) were positive at a titre of 1:160 with a homogeneous pattern. Extractable nuclear antigen and anti-dsDNA antibodies were negative and complement levels were within the normal range. A diagnosis of late-onset SLE was made according to the 2019 ACR/EULAR criteria. Hydroxychloroquine dosage was increased to 400 mg/day. Prednisone 0.5 mg/kg/day was started and progressively decreased to a maintenance dose of 5 mg/day. The patient remained clinically stable for one year, but during the following three years the polyarthritis reactivated and multiple types of skin lesions appeared, which were consistent with generalised urticarial vasculitis, neutrophilic dermatosis with pustular sterile lesions on the hands and feet (Fig. 1B-C), and recurrent inflammatory nodules in the lower extremities with a histopathological pattern of septal panniculitis. In parallel, laboratory tests got progressively worse (haemoglobin 8.7 g/dL; ESR 119 mm/hr, leukocytes 2,100/µL; lymphocytes 100/µL). Oral prednisone was increased again to 30 mg/day. Multiple treatments were attempted (methotrexate, belimumab, rituximab, mycophenolate mofetil) obtaining a partial response but with none of them it was possible to reduce the dose of prednisone below 15 mg/day. Taking into account the age of the patient, the refractoriness to multiple treatments and the appearance of a biclonal IgG kappa and lambda gammopathy on the proteinogram, the possibility of VEXAS syndrome was considered. Sequencing of UBA1 gene was performed using genomic DNA from peripheral blood leukocytes, identifying the variant c.121A>C p.(Met41Leu). According to the clinical manifestations and the laboratory and histopathology results, a diagnosis of VEXAS syndrome was finally made.

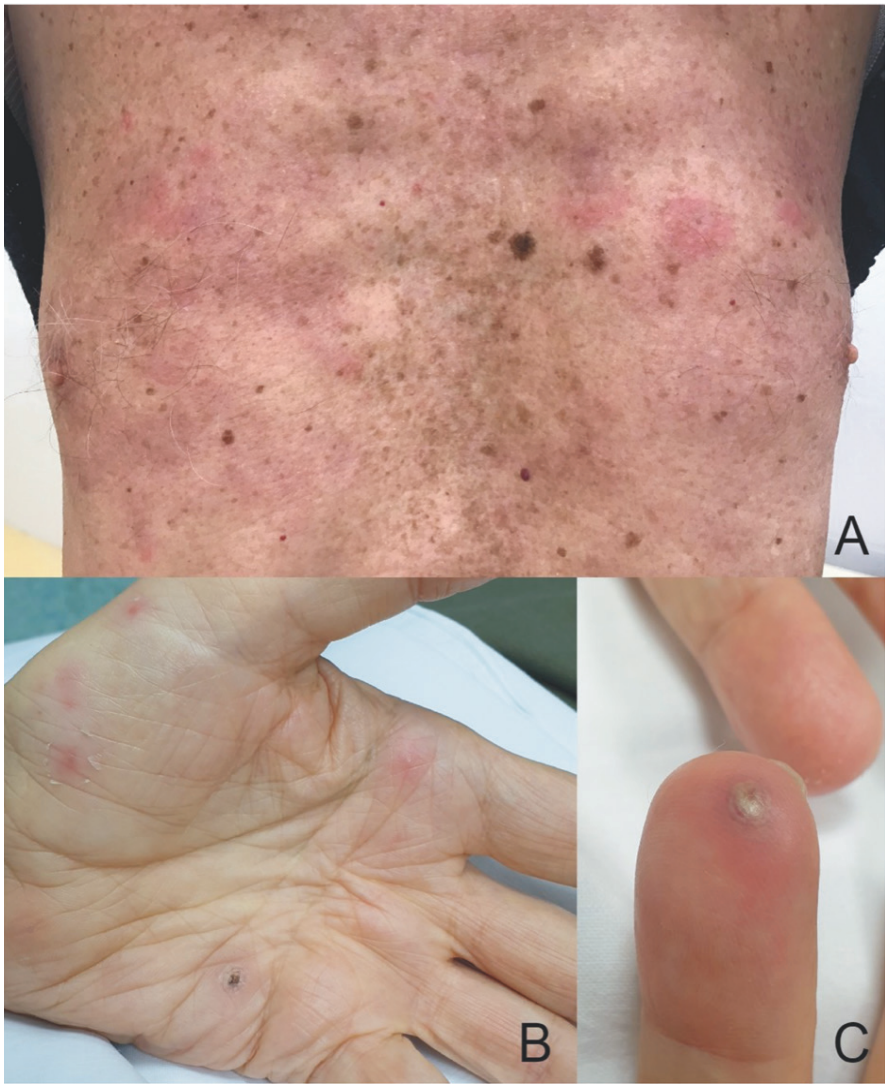


**Fig. 1A**. Lupus tumidus; **B**-**C**: neutrophilic dermatosis.

VEXAS syndrome presents with very heterogeneous and still not fully defined clinical manifestations. The two large published cohorts describe different phenotypes and many of them overlap with classic inflammatory diseases such as relapsing polychondritis, Sweet's syndrome, polyarteritis nodosa or giant cell arteritis (1,2). Isolated cases of patients with other rheumatological diagnoses such as erosive rheumatoid arthritis or HLA-B27 spondyloarthritis refractory to treatment finally diagnosed with VEXAS syndrome have been described (4, 5). To our knowledge, only one case of SLE in the elderly finally diagnosed with VEXAS syndrome has been described. Both patients share joint, cutaneous and haematological dominance, ANA positivity, meet the 2019 ACR/EULAR criteria for SLE, were refractory to multiple treatments and have the same UBA1 gene mutation (c.121A>C p.(Met41Leu)) (6).

The different phenotypes described in VEXAS syndrome make us reflect. Some patients behave as if they had VEXAS syndrome from the onset of symptoms (typically elderly patients presenting with inflammatory and haematological manifestations that are highly refractory to treatments), but others make us doubt whether they are patients with a previous rheumatic disease who, at a

given moment, suffer the mutation and develop another inflammatory syndrome. Case reports like the present one will help to better understand the pathophysiology of this complex disease.

M. Sallés[1], *MD*
X. Fustà[2], *MD*
L. Creus[2], *MD*
M. Esquius[2], *MD*
S. Mínguez[1], *MD*

*[1]Department of Rheumatology, [2]Department of Dermatology, Althaia Xarxa Assistencial Universitaria Manresa, Barcelona, Spain.*

*Please address correspondence to:*
*Meritxell Sallés*
*Department of Rheumatology,*
*Althaia Xarxa Assistencial*
*Universitaria Manresa,*
*C/ Dr. Joan Soler 1-3,*
*08243 Manresa, Barcelona, Spain.*
*E-mail: msallesl@althaia.cat*
*ORCID iD: 0000-0002-3721-645X*

*Competing interests: none declared.*



## References

1. BECK DB, FERRADA MA, SIKORA KA *et al.*: Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. *NEJM* 2020; 383(27): 2628-38. https://doi.org/10.1056/nejmoa2026834
2. GEORGIN-LAVIALLE S, TERRIER B, GUEDON AF *et al.*: Further Characterization of clinical and laboratory features in VEXAS syndrome: large-scale analysis of a multicentre case series of 116 French patients. *Br J Dermatol* 2022; 186(3): 564-74. https://doi.org/10.1111/bjd.20805
3. FERRADA MA, SAVIC S, CARDONA DO *et al.*: Translation of cytoplasmic UBA1 contributes to VEXAS syndrome pathogenesis. *Blood* 2022; 140(13): 1496-506. https://doi.org/10.1182/blood.2022016985
4. MAGNOL M, COUVARAS L, DEGBOÉ Y *et al.*: VEXAS syndrome in a patient with previous spondyloarthritis with a favourable response to intravenous immunoglobulin and anti-IL17 therapy. *Rheumatology* 2021; 60(9): e314-5. https://doi.org/10.1093/rheumatology/keab211
5. LACOMBE V, KOSMIDER O, PRÉVOST M, LAVIGNE C, URBANSKI G: Severe joint involvement in VEXAS syndrome: a case report. *Ann Intern Med* 2021; 174(7): 1025-7. https://doi.org/10.7326/L21-0023
6. SHARMA A, NAIDU G, DEO P, BECK DB: VEXAS syndrome with systemic lupus erythematosus: expanding the spectrum of associated conditions. *Arthritis Rheumatol* 2022; 74(2): 369-71. https://doi.org/10.1002/art.41957